

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK

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IN RE: :  
: 17-MD-2767 (PAE)  
MIRENA IUS LEVONORGESTREL-RELATED : 17-MC-2767 (PAE)  
PRODUCTS LIABILITY LITIGATION (NO. II) :  
: 17-MC-2767 (PAE)  
*This Document Relates To All Actions* :  
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**PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE**  
**EXPERT TESTIMONY OF PHILIP DARNEY, MD, MSc**

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## **FACTUAL BACKGROUND**

Levonorgestrel (LNG) is a potent synthetic progestin.<sup>1</sup> *See* Dfts. Br. 2, “Factual Background” (The Mirena IUD “consists of a T-shaped plastic frame with a reservoir that releases LNG, a progestogen steroid hormone.”). Although Mirena *generally* releases lower daily doses of LNG than other levonorgestrel-containing contraceptives, and – according to Bayer – it “mainly localizes in the patient’s uterine cavity.” *Id.*, the resulting serum level of LNG, and resultant profile of systemic side effects in individual women, is far from simple. First, “[m]etabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG-containing contraceptive products.” Ex. A, Mirena Label 2015 Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc., October 2015 (hereinafter, “2015 Mirena Label”). Serum (*i.e.*, systemic) LNG levels vary greatly both inter- and intra-individually, regardless of the method of administration. *See generally* Ex. B, Kenneth Fotherby. *Levonorgestrel*, 28 CLIN. PHARMACOKINET 203-215 (1995).

The expected side-effect profile of Mirena compared to other LNG-containing contraceptives is further complicated and magnified by pharmacological principles of steroid hormone activity. Steroid hormones such as LNG induce or inhibit various activities in the human body – both desired contraceptive action, and adverse effects such as acne – by binding at steroid hormone receptors within cells at the target organs. *See generally* Ex. C, A. Phillips, D.W. Hahn and J.L. McGuire, *Relative binding affinity of norgestimate and other progestins for human sex hormone-binding globulin*, 55 Steroids 373-375 (1990). Concurrently, sex hormones also bind with varying affinity to the transport proteins albumin and sex hormone binding globulin (SHBG).

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<sup>1</sup> Progestin is one of many names for a class of synthetic sex hormones (such as LNG) derived from testosterone, with the desired effect of progesterone (the natural female steroid hormone responsible for both preventing and maintaining pregnancy). Other names for this group of hormones include progestogens (*e.g.*, Dfts. Br. 2) and gestagens (*e.g.*, Ex. A8, Fotherby K. *Levonorgestrel*. Clin Pharmacokinet. 28 (3): 203-15. 1995 (hereinafter, “1995 Fotherby”).

*Id.* Prevailing principles of cellular biochemistry provide that the fraction of the sex hormone bound to SHBG is thereby “occupied” and incapable of binding to receptors, and hormonal activity is therefore limited to the degree of binding to SHBG. *See, e.g.*, November 21, 2017 30(b)(6) Deposition of Birte Hofmann (“Hoffman 30(b)(6) Tr.”), attached as Ex. D, at 294:11-294.22.

Therefore, the free (*i.e.*, unbound) fraction of the sex hormone is highly relevant to predicting its resulting activity. Ex. E, Carl M. Mendel, *The Free Hormone Hypothesis: A Physiologically Based Mathematical Model*, 16 Endocrin Rev 232-274 (1989); *see also* Ex. F, MIR\_JR\_00183776, 05/11/2004 Statement on the use of FLI (free levonorgestrel index) for comparison of different estrogen/LNG combinations<sup>2</sup> (“Based on these facts, the unbound or free fraction of LNG are considered to be more important for any comparison between different estrogen/LNG combinations.”)

While Mirena contains *only* LNG, nearly every LNG-containing oral contraceptive marketed in the United States contains an estrogen component, commonly in the form of ethinyl estradiol (EE). *See* U.S. Department of Health and Human Services, FDA Drug Database search results, Norgestrel.<sup>3</sup> “Administration of [LNG] alone markedly reduces serum SHBG levels and causes a concomitant decrease in SHBG-bound levonorgestrel”; however, “when the same dose [is] given with ethinyl estradiol, the reverse occur[s], *i.e.*, a minor increase in SHBG and SHBG-bound levonorgestrel[.]” Fotherby, at 207. Correspondingly, when administered alone, more LNG is “free”, and therefore capable of binding to steroid hormone receptors, and inducing or inhibiting biological activity. Therefore, although Mirena use *generally* “results in lower circulating levels of LNG than do other LNG-containing contraceptives” (Dfts. Br. 2-3), its capacity to induce

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<sup>2</sup> Dr. Christian Zurth served as Senior Pharmacokinetics Expert in Women’s Healthcare for Bayer and its predecessors until 2012. He was deposed as a fact witness in this litigation on November 29, 2017.

<sup>3</sup> Search executed March 15, 2018. Available at <https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

hormonal action or biological activity in the body is not necessarily – or simply – dose-dependent. Ex. G, Ayman A. A. Ewies, *Levonorgestrel-releasing Intrauterine System – The discontinuing story*, GYNECOL ENDOCRINOL. 668-673 (2009), (“There are large variations among different studies as regards the mean LNG concentrations after administration of the same dose of LNG, and there is insufficient data to show whether there is a correlation between dose and serum concentrations.”).

Finally, “[a]n ideal progestin should achieve a progestational response when given at a low concentration but elicit an androgenic response only at a high concentration.” Ex. H, Philip Darney, *The Androgenicity of Progestins*, 98 Am. J. Med. (1995) at 1105S. Because LNG binds significantly to *every* steroid hormone receptor with varying affinity – particularly to the androgen receptor – it exhibits substantial hormonal activity even at a low concentration. *Id.*; *see also* Ex. I, MIR\_PIEU-R\_00377654, Bayer Expert report on the toxico-pharmacological documentation to the Mirena NDA (“LNG is not a pure progesterone agonist. It has a low, but substantial affinity to the androgen receptor and the mineralocorticoid receptor, and to some transport proteins.”)

Even Population Council scientist, Dr. Regine Sitruk-Ware,<sup>4</sup> has described this chemical process in the medical literature. *See e.g.*, Ex. J, Regine Sitruk-Ware, *New progestagens for contraceptive use*, HUM REPROD. 169-178 (2006); (“[t]he effects of progestins are related to interactions not only with the progesterone receptor (PR) but also with other steroid hormone receptors. Some progestins interact with the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR) or the mineralocorticoid receptor (MR).”) Binding to these receptors “may either induce transactivation of a steroid receptor or prevent activation. In the target organ, the balance between the receptor coactivators and corepressors recruited by a progestin

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<sup>4</sup> Population Council was the original sponsor of the Mirena New Drug Application (hereinafter, “NDA”), later transferred to Bayer Healthcare. Dr. Sitruk-Ware has also served as a paid consultant for Bayer Healthcare.

determines whether the overall effect of the molecule will be agonistic or antagonistic.” *Id.* Therefore, the common adverse effects of LNG that are included on the Mirena label are directly attributable to these hormone-receptor interactions,<sup>5</sup> as acknowledged by even Bayer. *See, e.g.* Hoffman 30(b)(6) Tr., at 167:4-16; 340:1-12.

Unsurprisingly, Bayer researchers have attempted to develop a “New Progestin” for contraceptive use, designed for superior “dissociation of local vs. systemic” side effects. Ex. K, U.S. Patent Application Publication No. US 2015/0065472 A1 (43) (published Mar. 5, 2015), at p. 11. *See also* Ex. L, MIR\_CH-R\_00085086, 09/22/2010 Meeting Minutes, at -5089 (“The dissociation of local vs. systemic progestogenic activity provided by BAY 1007626 is expected to address liabilities of Mirena or LCS as outlined by research”); Ex. M, MIR\_HC-R\_00013317, 2010 Masterplan Project Description, at -3319 (Project Rationale. “Undesired effects of MIRENA® concern systemic effects such as ovarian cyst formation, acne, and breast tenderness. These side effects are due to the systemic availability of Levonorgestrel.”) Clearly, as opined by Dr. Darney and as Bayer well knows, the circulating levels of LNG provided by Mirena, and Mirena’s corresponding side effect profile, are far from *de minimis*.

#### **PRELIMINARY STATEMENT ON DR. PHILIP DARNEY, MD, MS**

Dr. Phillip Darney, MD, MSc intends to offer expert testimony on the following opinions:

1. Levonorgestrel (LNG) is a potent androgenic progestin.
2. Intrauterine delivery of LNG, compared to other routes, *e.g.*, oral, subdermal and transdermal, results in wide intra- and inter-individual serum concentrations of LNG.

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<sup>5</sup> For example, acne and ovarian cysts (> 5% reported in clinical trials) are evidence of androgenic activity. 2015 Mirena Label, at 15. Edema (swelling) (<5% reported in clinical trials) is evidence of mineralocorticoid activity. *See* Ex. A, Mirena [prescribing information] at p. 14.

3. Individual women vary greatly in their physiologic reactions to LNG, regardless of the route of administration.
4. In susceptible individuals, relatively high unbound LNG concentrations can cause, or be a substantial contributing factor in causing pseudotumor cerebri (PTC).

Bayer, in its Motion to Exclude Dr. Darney, has substantially mischaracterized Dr. Darney's opinions, and the basis on which he forms those opinions. *See*, Bayer's Motion to Exclude Dr. Philip Darney (hereinafter Mot. Exclude Darney). In fact, Bayer ignores the bulk of Dr. Darney's report, instead focusing on specific citations and portions of his report to attack his ultimate conclusion that LNG can cause or contribute to PTC.

Dr. Darney is a practicing OBGYN, and has vast training and experience in epidemiology, endocrinology, and clinical trial development. *See* Ex. N, General Causation Expert Report of Philip Darney, MD, MSc (hereinafter Darney Ex. Rpt.), at 1-3. Dr. Darney has worked and continues to work with Bayer on a number of studies and trials. *Id.* He has conducted over 100 clinical trials, many of these for Bayer, focused solely on family planning and contraception. Darney Ex. Rpt., at 3. As Bayer and its experts readily point out, Dr. Darney literally wrote the book on clinical contraception. *See* Leon Speroff & Philip Darney, A CLINICAL GUIDE FOR CONTRACEPTION (2011 5th ed.). For many years, Dr. Darney has been a thought-leader and world renowned expert in contraception, including steroid hormonal contraception like Mirena. *See, e.g.* Ex. O MIR\_RB\_00016938 ("Dr. Darney is a key thought leader, and is a huge Mirena advocate.").

Bayer correctly acknowledges that Dr. Darney has long been a proponent of LARC-styled contraceptives. Mot. Exclude Darney, at 3. However, Bayer mischaracterizes this support for Mirena as contradictory to his opinions in this case. The fact that Dr. Darney has long been a proponent of LARCs, including Mirena, lends credence to his opinions. Darney Ex. Rpt., at 5. Dr.

Darney does not have any bias against Bayer or Mirena, and, as a result, has performed an unbiased, scientific analysis of the available evidence. As Dr. Darney explains in his report, fully informing physicians and patients about the risks of Mirena is his ultimate priority, not blindly protecting a legacy contraceptive product by masking a risk of the product. Darney Ex. Rpt., at 23.

Bayer's own experts in this litigation have repeatedly expressed praise for Dr. Darney, his work, and his abilities as a practitioner, researcher, and teacher. They have also attested to his lack of bias. For example, Dr. Dana Gossett testified that "Dr. Darney has no bias against any particular product or method . . . including Mirena." Ex. P, February 14, 2018 Deposition Transcript of Dana Gossett ("Gossett Tr.") at 193:3-19. Likewise, when asked about her knowledge of Dr. Darney, Bayer's expert witness Dr. Geri Hewitt noted:

I've not met him personally, but I recognize that he is highly respected in the field around contraception and family planning. I think historically he's been a thought leader in the field of contraception and family planning. I have known people that have -- that he's trained, and I've had high regard for them. I've always appreciated when I -- earlier in my career that I oftentimes would refer to his textbook. I thought his textbook was very helpful earlier in my career, and I oftentimes -- you know, I think it's been a while since they've updated it, the contraceptive technology textbook he and Speroff would do. I think I'm -- you know, I'm familiar with his reputation. . . . I would say that Phil Darney's reputation is that he is known for being very active and one of the initial sort of founders of the world of contraception and family planning. . . .

Ex. Q, February 9, 2018 Deposition Transcript of Dr. Geri D. Hewitt, M.D., (Hewitt Tr.) at 24:25-25:1-22.

### **STANDARD OF REVIEW**

Plaintiffs respectfully refer the Court to the legal standard set forth in detail in Plaintiffs' Omnibus Response and hereby incorporate that Omnibus Response into this Memorandum. In short, Federal Rule of Evidence 702 requires that expert testimony be "not only relevant, but reliable." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590 (1993). To be reliable, "[t]he subject of an expert's testimony must be 'scientific . . . knowledge.'" *Id.* at 589-90. Under

*Daubert*, “an expert need not base his opinion on the best possible evidence, but upon ‘good grounds, based on what is known.’” *Id.* at 590.

## **ARGUMENT**

### **I. Dr. Darney’s Opinions are based on a Reliable Foundation and Methodology**

Dr. Darney is unquestionably qualified to offer the opinions he is offering in this case. In fact, Bayer makes no attempt to refute his qualifications. Instead, Bayer levels an attack on specific, minute details of Dr. Darney’s opinions and a few selected pieces of evidence that support those opinions, with the apparent goal of undermining the entirety of Dr. Darney’s opinions. Put simply, Bayer makes an incomplete and often disingenuous attempt to refute Dr. Darney’s opinions.

Contrary to Bayer’s argument, Dr. Darney’s opinions are properly based on a reliable foundation. He has based his opinions on a thorough analysis of the current scientific literature, internal Bayer documents, and his years of clinical and scientific experience. Bayer would have this Court believe that Dr. Darney crafted his opinions based on a cherry-picked assortment of literature and data that supports his conclusions. This could not be farther from the truth, though it may seem that way from the citations and deposition testimony cherry-picked by Bayer for its Motion to Exclude.

Before even agreeing to serve as an expert for Plaintiffs, Dr. Darney conducted his own independent literature search on Mirena, PTC, and LNG, in order to determine if the issue warranted his further investigation. Ex. R, January 30, 2018 Deposition Transcript of Dr. Philip Darney, MD, MSc (hereinafter “Darney Tr.”) at 14:23-25. After agreeing to serve as an expert for the Plaintiffs, in preparing his report, Dr. Darney consulted and relied on a broad array of evidence, including: 1) 58 separate medical and scientific articles (Darney Rpt. at “Sources”); 2) textbooks co-authored by Dr. Darney (Darney Tr. at 21:7-25); 3) relevant drug labels for Jadelle, Kyleena,

Mirena, Norplant, and Skyla (Darney Rpt. at “Sources”; Darney Tr. at 24:13-25:7); and 4) deposition transcripts of two Bayer employees, Birte Hofmann and Christian Zurth (Darney Rpt. at “Sources”; Darney Tr. at 27:12-28:4). Dr. Darney also consulted forty-seven separate internal Bayer documents in forming his opinions, Darney Rpt. at ‘Sources”; Darney Tr. at 23: 10-15, as well as adverse event reports and “[i]nformation about subjects and clinical trials of Mirena in which I participated in the past . . .” Darney Tr. at 24:2-7.

In addition to this wealth of evidence, Dr. Darney also relied heavily on his own background knowledge and experience, including his prior experience with LNG, PTC and Mirena. As Dr. Darney notes, he himself investigated the link between Norplant and IIH/PTC back in the 1990s—he recalled “disuss[ing] this issue in the past. So it wasn’t something . . . I was completely unfamiliar with.” Darney Tr. at 23:24-24:4. Dr. Darney even notes that he helped write the drafts of labels for Norplant and Jadelle “[d]uring the course of research . . . with the Population Council and subsequently with Wyeth.” Darney Tr. at 25:2-13.

Ignoring the substantial support for Dr. Darney’s opinions, Bayer attempts to atomize the separate components of Dr. Darney’s report.

Bayer ignores the weight of the evidence—the totality of which supports a causal relationship between Mirena use and PTC—and instead criticizes and attempts to discredit specific individual citations from Dr. Darney’s report. Bayer implies that: 1) Dr. Darney’s entire opinion relies on a single citation; and 2) that because *Bayer* has a criticism of the specific citations or Dr. Darney’s analysis of that citation, *all* of his opinions are unreliable. This is simply not an appropriate way to measure an expert’s opinions under *Daubert* and its progeny. *See Milward v. Acuity Specialty Prods. Group*, 639 F.3d 11, 23, 2011 U.S. App. LEXIS 5727, \*30-31. At times, the court’s error in excluding Dr. Smith’s testimony derived from a mistake in its understanding of

the weight of the evidence methodology employed by Dr. Smith. The court treated the separate evidentiary components of Dr. Smith's analysis atomistically, as though his ultimate opinion was independently supported by each. Dr. Darney has built a brick house, and each brick is a piece of scientific evidence. Bayer urges that the entire house should come crashing down if there are some minor imperfections on a few of the bricks. This is simply not an appropriate *Daubert* analysis. *See, e.g. General Electric Co. v. Joiner*, 522 U.S. 136, 153-55 (1997) (Stevens, dissenting) ("It is not intrinsically unscientific for experienced professionals to arrive at a conclusion by weighing all available scientific evidence—this is not the sort of 'junk science' with which *Daubert* was concerned . . .").

A glaring example of Bayer's atomistic approach to undermining Dr. Darney's opinions is the discussion of Glueck 2005. Mot. Exclude Darney at p. 7. Bayer states that "Dr. Darney relies on Glueck 2005 to support his androgen hypothesis." *Id.* Importantly, The Glueck study is not the entire basis for any of Dr. Darney's opinions, as Bayer implies. Instead, Glueck is only one of many pieces of evidence that Dr. Darney relies on in forming his opinions. Bayer goes on to mischaracterize Dr. Darney's deposition testimony and argue that Dr. Darney's opinion about Glueck is "based on a 'suggestion' of an 'implication' from an article that itself was 'speculating' about a different hormone." *Id.* Initially, Bayer's intention here is clearly to cast doubt on Dr. Darney's opinions by emphasizing words like "suggestion", "implication" and "speculating." However, the *Daubert* analysis requires more than just semantics. Further, in his deposition, Dr. Darney thoroughly explained the value of Glueck as *one of the pieces of evidence* that supports his ultimate opinions. Darney Tr. at 246:22-251:22; 251:20-22. Unfortunately, Bayer's argument focuses only on the semantics and ignores the explanation provided by Dr. Darney. This is a complex scientific question that requires complex analysis of many pieces of evidence, and all of

these pieces of evidence do not individually “establish” the causal relationship between LNG and PTC. It is Dr. Darney’s task as a scientist is to reach a conclusion based on all of the evidence available to him, including evidence about the relationship between steroid sex hormones and PTC. This complex task of synthesizing all the available evidence is the task of a scientist, not of Bayer’s attorneys. Dr. Darney ultimately testified about Glueck that “[i]t does not say that androgens cause – and you wouldn’t expect that the explanation would be that simple – cause pseudotumor cerebri....” Darney Tr. at 251:20-22.

Another example of Bayer’s atomistic approach is its argument that Dr. Darney’s opinions are unreliable because he read the 2015 Etminan article after he finalized his report. As Bayer notes, “Dr. Darney did not even review Etminan [2015], the only other epidemiology study available concerning Mirena and IIH, until *after* he completed his report.” Mot. Exclude Darney, at 13. Bayer, quoting language from *In re Rezulin Prods. Liab. Litig.*, asserts that Dr. Darney’s opinions were formed based on the expediencies of this particular litigation.” *In re Rezulin Prods. Liab. Litig.* 309 F. Supp. 2d 531, 562-63 (S.D.N.Y. 2004). Nothing could be farther from the truth.

In *Rezulin*, the court properly excluded the expert from testifying as to certain topics because they had failed to consider two studies that addressed the subject of the litigation. *Id.* at 563. The court notes that the expert in *Rezulin* thus violated his own methodology by failing to take into account all relevant evidence. *Id.* The distinction here, however, is that Dr. Darney did take into account all relevant and reliable evidence; but he did not rely on the Etminan article because he did not believe it was reliable. See Darney Tr. at 207:2-214:3.

Dr. Darney admits the he selectively chooses what evidence to rely on in forming his opinions, based on what is reliable. Darney Tr. at 33:16-34:9. But that is precisely what leads to a reliable foundation for expert opinions. The idea that Etminan 2015 is unreliable is not only posited

by Dr. Darney, but by Defendant's own experts as well. Dr. Gossett, in her deposition, stated the following when asked about the 2015 Etminan article: "I do not believe that this study is a reliable study due to a variety of design flaws." Gossett Tr. at 148:6-7. To argue that Dr. Darney should be excluded for not relying on an unreliable study in drafting his report while Defendant's own expert admitted the very same concerns about this study is disingenuous. Dr. Darney did not ignore reliable, relevant evidence, as the expert in *Rezulin* did. He instead chose to focus only on reliable evidence in forming his opinions.

Another example of Bayer's atomistic approach is its argument regarding the 2017 Valenzuela study. Bayer, criticizes Dr. Darney's reliance on Valenzuela, quoting *Rosen v. Ciba-Geigy Corp.*, for the proposition that "an expert who supplies nothing but a bottom line supplies nothing of value to the judicial process." 78 F.3d 316, 319 (7th Cir. Ct. App. 1996). It must be emphasized that Dr. Darney does not rely exclusively on Valenzuela. He cites Valenzuela as further evidence supporting a causal relationship between LNG and PTC, stating that "[i]n light of scientific and medical evidence supporting a biologically plausible causative role for androgenic steroids such as LNG, this data strongly supports the conclusion that Mirena and LNG can cause, or be a substantial contributing factor in causing, PTC. Darney Ex. Rpt. at 23. Clearly, Dr. Darney has not supplied merely a "bottom line," as Bayer argues. Instead, he has cited to a peer-reviewed published study as further support for his overall causation opinion.

Bayer also claims that "Dr. Darney conceded that Valenzuela 'does not prove' a causal relationship, but nevertheless insisted that Valenzuela still 'suggests' a causal relationship." Mot. Exclude Darney at 12. By stating this, Bayer argues that Dr. Darney has gone "beyond the stated conclusions of the authors of Valenzuela that 'our investigation . . . does not suggest an LNG-IUS can cause PTC.'" Mot. Exclude Darney at 12. Despite Bayer's criticism, Dr. Darney simply

reviewed the study critically and assessed it for its strengths and weaknesses. And again, he relied on Valenzuela as one piece of evidence in the overall weight of the evidence analysis.

Dr. Darney notes in his testimony that he believes that “some of the biases in [the Valenzuela authors’] own work that they assert are – are patently wrong.” Darney Tr. at 183:15-22 (noting that the authors’ assertion that COCs are not a treatment for polycystic ovarian syndrome is incorrect—it is the other way around). Further, Dr. Darney had this to say about the Valenzuela study’s conclusion that their investigation does not suggest a Mirena can cause IIH/PTC:

Q. And because of the various confounders in other issues, the Valenzuela authors actually conclude that their investigation does not suggest an LNG-IUS can cause PTC.

Did you see that in --

A. Yes, I see that.

Q. And you agree with that, don't you, Doctor?

THE WITNESS: Well, as I said, I think they've been a little harsh on themselves with regard to these possibly androgenic -- possibly and clearly androgenic conditions -- headache, possibly. Polycystic ovarian syndrome, clearly -- who are less, not more likely, to receive levonorgestrel system. So on the one hand, they have biases. On the other, I think they misjudge the degree to which their results are biased.

Darney Tr. at 185:19-186:5. Dr. Darney, after critically reading this piece, notes that it is his opinion that the authors have misjudged some of the results obtained based on their biases and confounders. *Id.* Dr. Darney also admits that the Valenzuela “study does have some limitations.” *Id.* at 186:13-14. Likewise, when asked whether he agrees with the Valenzuela authors’ conclusion that an LNG-IUS can cause PTC, Dr. Darney states:

THE WITNESS: I think it suggests a relationship. It does not prove one.

BY MS. COOK:

Q. Okay. And -- and just to be clear, the relationship I'm talking about is a cause-and-effect relationship. Do you believe that the Valenzuela article suggests a cause-and-effect relationship?

THE WITNESS: I agree that it suggests one.

BY MS. COOK:

Q. And that's a different finding than the study authors themselves; right?

THE WITNESS: Yes.

Darney Tr. at 187:14-188:3. Additionally, when asked if he was “giving the opinion that Valenzuela is evidence that Mirena causes IIH,” Dr. Darney testified that Valenzuela was supportive evidence for his causation opinion, but not conclusive. Darney Tr. at 192:15-193:12. Bayer returns to this atomistic and semantic arguments, implying that one piece of evidence does not “prove” causation.<sup>6</sup> In response to this flawed argument, Dr. Darney summarizes his thoughts on Valenzuela by stating “[b]y itself, it’s not evidence that Mirena causes PTC and that’s why it’s not the only reference that’s cited in my report. I think you have to look at the evidence in its entirety.” *Id.* at 193:24-194:2.

None of this testimony suggests even in the slightest that Dr. Darney has “exceeded the limitations” the Valenzuela authors concluded from their work. As noted above, Dr. Darney believes that the Valenzuela piece, like the entirety of the other evidence he relied on—as shown above—is simply one piece in an overarching picture that shows a causal relationship between LNG and the development of IIH. *See* Darney Tr. at 194:1-2. Contrary to Bayer’s argument, Dr. Darney’s method in forming his expert opinions in this litigation is exhaustive. He has not cherry-picked evidence that supports his conclusion—instead, he has looked at a totality of evidence, including medical and scientific literature, internal Bayer documents, and his own vast experience both as a clinician and as a researcher. Nevertheless, Bayer nitpicks his opinions and methodology, and insists that Dr. Darney’s opinions do not pass the well-established *Daubert* standard. Bayer’s incomplete and atomistic arguments do not successfully undermine Dr. Darney’s opinions, nor do they change the fact that Dr. Darney’s opinions are appropriately supported by reliable methodology and foundation.

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<sup>6</sup> *See, e.g. Zuchowicz v. United States*, 870 F. Supp. 15, 20 (D. Conn. 1994). As will be discussed, Bayer urges a standard of proof that is not even accepted in the realm of science. It argues, as a consistent theme, that something must be “proven” or “established” to be admissible. This level of certainty is not possible or required in the scientific arena, and is certainly not required in the legal system. *Id.*

**II. Bayer Misinterprets the Requirements of *Daubert* in Arguing for Exclusion of Dr. Darney's Opinions on Mechanism of Injury**

Bayer claims that Dr. Darney's opinions on a biologically plausible mechanism relating to androgenic effects does not pass *Daubert*. See Mot. Exclude Darney, at 4-5. Essentially, Bayer argues because Dr. Darney's opinion has not met every guideline set forth in *Daubert*, his opinions should be excluded. Bayer's insistence that Dr. Darney's opinions should be excluded because they fail to meet all four factors set forth in *Daubert* is a misapplication of *Daubert* and its progeny. As the Court in *Daubert* originally noted, the test envisioned by F.R.E. 702 is not a rigorous factor test, but rather, a “flexible one.” *Daubert*, 509 U.S. at 594. Four years later, in *Kumho Tire Co. v. Carmichael*, the Court unequivocally stated “*Daubert* makes clear that the factors it mentions do not constitute a ‘definitive checklist or test.’” 526 U.S. 137, 150 (1999) (quoting *Daubert*, 509 U.S. at 593). The Court further emphasized that the “gatekeeping inquiry must be ‘tied to the facts’ of a particular ‘case.’” *Id.* at 150 (quoting *Daubert*, 509 U.S. at 591).

An expert's inference or assertion must, then, “be derived by the scientific method in order to qualify as ‘scientific knowledge.’” *Id.* As case law makes clear, “it would be unreasonable to conclude that the subject of scientific testimony must be ‘known’ to a certainty; arguably, there are no certainties in science . . . ‘Indeed, scientists do not assert that they know what is immutably ‘true’ – they are committed to searching for new, temporary, theories to explain, as best they can, phenomena.’” *Zuchowicz v. United States*, 870 F. Supp. 15, 20, (D. Conn. Sep. 15, 1994) (quoting *Daubert*, 509 U.S., at 590). Thus, “[s]cience is not an encyclopedic body of knowledge about the universe. Instead, it represents a *process* for proposing and refining theoretical explanations about the world that are subject to further testing and refinement” *Daubert*, 509 U.S., at 590 (quoting Brief for American Association for the Advancement of Science et al. as *Amici Curiae* 7-8) (emphasis in original).

Likewise, under *Daubert*, “an expert need not base his opinion on the best possible evidence, but upon ‘good grounds, based on what is known.’” *Deutsch v. Novartis Pharms. Corp.*, 768 F. Supp. 2d 420, 453 (E.D.N.Y. Mar. 8, 2011) (quoting *Daubert*, 509 U.S. at 590). This is precisely what Dr. Darney has done in this litigation, as shown below.

**First**, Bayer argues “Darney has never tested his opinion with direct experimentation, epidemiological studies, clinical trials or any other method of testing. Mot. Exclude Darney, at 4. Bayer also argues that because of the lack of testing on the part of Dr. Darney, he is unable to produce a “known error rate.”<sup>7</sup> Mot. Exclude Darney at 4-5.

There is no *Daubert* requirement that Dr. Darney perform the testing on the choroid plexus himself, let alone develop an entire study structure to determine the plausibility of the androgen mechanism and produce a reasonably accurate error rate. As the Supreme Court in *Daubert* stated, “[u]nlike an ordinary witness . . . an expert is permitted wide latitude to offer opinions, including those that are *not based on firsthand knowledge or observation*. 509 U.S. at 592 (emphasis added). *Daubert* does not require Dr. Darney to have developed and run the tests; if it did, Defense experts would have been required to as well, and as Dr. Johanson explained in his deposition testimony, Bayer itself has yet to run any tests. Johanson Tr. at 15:24-16:6.<sup>8</sup>

**Next**, because “Dr. Darney has never published his opinions in the peer-reviewed literature or anywhere outside of his expert report[,]” Bayer believes he should be excluded. Mot. Exclude Darney at 5. While it is true that Dr. Darney has never published his opinions on the androgenic mechanism and a causal relationship between Mirena and PTC, Dr. Darney has written over 300

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<sup>7</sup> Dr. Johanson, another Plaintiff expert, expressed shock that Bayer had not taken the time to research and test the choroid plexus, and noted that subcontracted out, Bayer could perform this research and testing, thereby answering some pivotal questions. January 26, 2018 Deposition Transcript of Dr. Conrad Johanson, Ph.D. (excerpts attached as Ex. T) at 15:12-17:5. However, this has nothing to do with Dr. Darney, despite Bayer’s attempt to confuse the matter.

<sup>8</sup> If it is possible to answer certain questions by performing testing, Bayer is the appropriate party to conduct those tests. This is especially true in light of the fact that Bayer still sells Mirena without any warning to patients about PTC.

scholarly articles on obstetrics, gynecology, contraception, and LARCs—many exploring LNG and its properties. Darney Tr. at 13:1-9. Of significance, Dr. Darney has published literature specifically on the androgenic propensity of LNG, research that he relies upon in reaching his opinions in this case. *See, e.g.* Philip Darney, *The Androgenicity of Progestins*, 98 Am. J. Med. (1995). In fact, Dr. Darney’s opinion that “LNG is the most potent and androgenic of the progestins used in contraceptives” is based on this published research. *See* Darney Ex. Rpt., at 9.<sup>9</sup>

**Finally**, Bayer seeks to exclude Dr. Darney under *Daubert* because he “admits that ‘it’s not *generally accepted* that [Mirena] causes [IIH].’” Mot. Exclude Darney at 5 (emphasis added). A reading of the *Daubert* opinion, however, notes that “[n]othing in the text of [Rule 702 of the Federal Rules of Evidence] establishes ‘general acceptance’ as an absolute prerequisite to admissibility.” *Daubert*, 509 U.S. at 588. Quite the opposite in fact, as case law below shows.

Contrary to Bayer’s protestations, a mechanism need not be definitively established or generally accepted to be admissible under *Daubert*. “Biologic plausibility is a judgment about whether an agent *plausibly* could cause a disease, based on existing knowledge about human biology and disease pathology. *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 181 (S.D.N.Y.) (citing Michael D. Green et al., Reference Guide on Epidemiology at 388 in Federal Judicial Center, Reference Manual on Scientific Evidence (2d Ed. 2000)) (emphasis added).

Likewise, “[t]hat the mechanism remains unknown does not mean that the one proposed by the [plaintiffs’ experts] is not widely accepted as plausible.” *Fosamax*, 645 F. Supp. 2d at 183 (citing *In re Neurontin Mktg. Sales Practices and Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 149 (D.Mass. 2009) (finding that biologic plausibility supported opinion on causation despite the fact that there was ‘robust debate in the scientific community’ on the proposed mechanism); *In re PPA*

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<sup>9</sup> Bayer does not seek exclusion of Dr. Darney’s opinion that LNG is a potent and androgenic progestin. This is likely because Bayer does not dispute that this is a fact. *See, e.g.* MIR\_JSEU\_01362341.

*Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003) (“The fact that the mechanism remains unclear does not call the reliability of the opinion into question.”). *Deutsch v. Novartis Pharm. Corp.*, 768 F. Supp. 2d 420, 438, 2011 U.S. Dist. LEXIS 22755, \*47-48 (citing *Fosamax*, 645 F. Supp. 2d at 198).

Bayer quotes Dr. Darney’s deposition, where he said “it’s not generally accepted that [Mirena] causes [IIH].” Darney Tr. at 201:15-20 (emphasis added). Dr. Darney, however, notes that for years there has been concern in the field of experts that Mirena *can potentially* cause IIH:

A. No, it’s not generally accepted that it causes it. There’s concern about the association.  
Q. Have you spoken to any expert in contraception about the concern about an association between Mirena specifically and IIH?  
A. Yes, I’ve talked to colleagues about it.  
Q. Who did you talk to?  
A. My colleagues who have done lots of research with levonorgestrel.  
Q. When did you --  
A. I mentioned two of them. Dan Mishell. Sam Pasquale.  
Q. When did you talk to them?  
A. As we were working on developing – doing our clinical trials for Mirena and outlining possible risk factors for androgen-sensitive women.  
Q. This was back in 2000?  
A. Yes.  
Q. Okay. So you were talking to certain colleagues about a potential concern about an association between Mirena and IIH as far back as 2000?  
A. Because we had been concerned about association -- case reports of an association with Norplant, where delivering levonorgestrel through a different system, should we have the same concerns about androgenic side effects.

Darney Tr. at 201:19-202:20.

Dr. Darney’s opinion on the biologically plausible mechanism by which LNG can cause PTC is relevant to the issue at hand, and is based on the totality of a substantial body of reliable evidence. The published literature that Dr. Darney relies upon is generally accepted, as is the methodology he has used to reach his opinions. Any criticisms or responses that Bayer has to the opinions can and should be presented at trial. *See, e.g. Daubert*, 509 U.S. at 596. (“Vigorous cross-

examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence.”). Bayer’s insistence that this opinion not only be “generally accepted,” but also adhere to all four guidelines set forth in F.R.E. 702 is a misstatement of the *Daubert* standard.

### **III. Bayer Does Not Seek Exclusion of Three of Four of Dr. Darney’s Opinions Offered in His Expert Report**

While Bayer, at times, seems to request wholesale exclusion of Dr. Darney’s opinions, its Motion sets forth no argument that the first three opinions listed in his report should be excluded. Specifically, Bayer does not argue for the exclusion of the following opinions: (1) LNG is a potent androgenic progestin; (2) Intrauterine delivery of LNG, compared to other routes, e.g., oral, subdermal and transdermal, results in wide intra- and inter-individual serum concentrations of LNG; or (3) Individual women vary greatly in their physiologic reactions to LNG, regardless of the route of administration. It is likely that Bayer does not attempt to exclude these opinions because they do not take issue with them. The androgenic capacity of LNG is well-documented in the literature and conceded by Bayer’s corporate designee. Hofmann 30(b)(6) Dep. at 59:1-15; 160:25-161:4; 165:16-20 (agreeing that binding to steroid receptors corresponds with biological effects); 167:4-168:10 (“Well, it is known that levonorgestrel has androgenic effects, so I assume -- well, it is also probably depending on the dose, but I assume that will be the reason why it could lead in some cases to acne, yes.”) *See also* Ex. S, MIR\_JSEU\_01362341 (“In comparison to other progestins, LNG is known to have a high binding affinity to androgen receptors causing androgenic side effects.”). Further, the LNG levels are admittedly variable. Hoffman 30(b)(6) Dep. At 71:13-72:2; *see also* Expert Report of Bayer expert witness William Jusko. Regardless of the reason, Bayer has not specifically criticized these opinions and, therefore, it is important to point out that

Bayer does not actually seek wholesale exclusion of Dr. Darney's testimony. Ultimately, Bayer only seeks exclusion of Dr. Darney's ultimate causation opinion.

#### **IV. Dr. Darney Accurately Addresses Contradictory Evidence**

Bayer criticizes Dr. Darney for, as they portray it, not explaining why LNG containing combined oral contraceptives ("COCs") and subdermal LNG implants, such as Norplant, are not linked to PTC, when they release an overall higher level of LNG into the system. Mot. Exclude Darney at 16-19. However, it is simply not true that Dr. Darney fails to address this issue. Dr. Darney's pharmacokinetics opinions, which Bayer does not challenge, address this very question. Specifically, Dr. Darney opines that "systemic LNG concentrations from intrauterine delivery systems like Mirena are much less predictable and stable than those from subdermal or oral administration." Darney Rept. at 16. Further, Dr. Darney did not foreclose the possibility of a causal relationship between Norplant and PTC, but testified that the available evidence does not support this causal relationship and that he does not intend to offer any opinion regarding this causal relationship. Darney Tr. 136:20-138:25. Similarly, when asked whether LNG-only oral contraceptives can cause PTC, Dr. Darney testified that he "wouldn't discard the possibility. I'm not aware of data that support the contention. *Id.* at 44:11-19. Ultimately, Dr. Darney forms conclusions based on available evidence and he has not reached the conclusion that Norplant or LNG-only oral contraceptives can cause PTC. However, this does not undermine his opinion that Mirena can cause PTC, which is based on a substantial body of evidence, as explained above. This is especially true in light of Dr. Darney's unchallenged pharmacokinetics opinions, which explain the important distinctions between Mirena and other LNG products.

Further undermining Bayer's argument regarding "contradictory evidence," a comparison between Mirena and LNG COCs is especially misplaced. As the Court is aware from Dr. Conrad Johanson's report, the hormonal homeostasis is disrupted by the introduction of LNG without an

estrogen component, ultimately leading to development of PTC. While a full discussion of this neurological mechanism of LNG induced PTC is beyond the scope of this Response, it is sufficient to say that comparing COCs, which contain an estrogen component, to Mirena is not helpful or relevant.

Bayer also levels a criticism of Dr. Darney's discussion of "estimates of free LNG calculated by Plaintiffs' counsel for a small handful of clinical trial patients selected by Plaintiffs' counsel." Mot. To Exclude Darney at 18. While it is true that Plaintiffs' counsel did provide Dr. Darney with calculated estimates of free LNG that he refers to in his report, he also reviewed the entire dataset of 3,000 clinical trial subjects. Darney Tr. 307:9-308:17. Further, he testified that the totality of the data supports his ultimate opinions on variability of LNG levels, not just the examples calculated by Plaintiffs' counsel. *Id.* Plaintiffs' counsel merely assisted Dr. Darney by making some calculations relating to free LNG levels and Bayer makes no challenge to these calculations. Bayer only raises this to imply that Plaintiffs' counsel has manipulated Dr. Darney's opinions; however, in light of Dr. Darney's testimony that he reviewed the entire dataset and that the totality of the data supports his opinions, Bayer's implication falls flat and even appears dishonest.

### **CONCLUSION**

Wherefore, Plaintiffs respectfully request that this honorable Court deny Bayer's Motion to Exclude the Expert Testimony of Phillip Darney, M.D., M.S.c.

Dated: March 15, 2018

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that on March 15, 2018, I served all counsel of record with the foregoing via this Court's CM/ECF System, which will provide notice of filing to all counsel of record.

/s/ *Martin D. Crump*  
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